



# **Exhibit 3**

# Epidemiologic Methods to Advance Our Understanding of Ovarian Cancer Risk

Holly R. Harris, ScD, MPH<sup>1,2</sup> ; Colette P. Davis, PhD, MSPH, MS<sup>3</sup> ; and Kathryn L. Terry, ScD<sup>4,5,6</sup>

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The use of intimate care products is a relatively common practice among women, with estimates of use in more than 50% in some populations.<sup>1-6</sup> Use of these products, including genital powder and douching, has been shown to vary across multiple factors including age, race, ethnicity, body size, and socioeconomic status.<sup>3,4,7,8</sup> These products are used for a variety of reasons including cleanliness, freshness, odor removal, and dryness of the genital region.<sup>4,9,10</sup> While use of these products is declining,<sup>11</sup> they are still available and their potential impact on long-term health needs to be clarified.

Ovarian cancer has been the most intensively studied in regard to intimate care product use and cancer risk—with the majority of the focus on genital powder use with inconsistent results. Pooled analyses of case-control studies have shown estimates of 24%–32% higher ovarian cancer risk for ever compared with never use of genital powder, as well as the suggestion of higher risk with increasing number of lifetime applications.<sup>2,5</sup> However, cohort studies, which have less detailed data on powder exposure (leading to nondifferential misclassification), have provided more ambiguous results, with limited power to detect modest associations even when data are pooled across studies.<sup>12-15</sup> Thus, given these previously identified differences by study design,<sup>16,17</sup> additional methods are necessary to more clearly understand the impacts of this common exposure on gynecologic and hormone-associated cancer outcomes.

In the article that accompanies this editorial, O'Brien et al<sup>18</sup> use a variety of methods to address the impact of bias and misclassification on the association between intimate care products (ie, genital powder use and douching) and ovarian cancer in the Sister Study, a prospective cohort of US women. These include quantitative bias analysis to examine different exposure reporting scenarios, as well as reclassifying exposures to address recall bias. O'Brien et al<sup>18</sup> also consider (1) exposures during different periods of life and (2) the associations between intimate care products and uterine and breast cancers which to date have been sparsely explored. Comparing the findings across these three hormone-associated cancer types, which share some, but not all, reproductive and anthropometric risk factors, provides an opportunity to untangle both potential biases (eg, exposure misclassification and recall bias) and elucidate potential biological mechanisms relevant to some of these cancers but not others.

After accounting for potential biases, O'Brien et al<sup>18</sup> report a significant increase in ovarian cancer risk for genital powder use, with effect estimates that are in range with previous studies.<sup>16</sup> The association is the strongest for genital powder exposure during the age ranges of 20s and 30s with similar increased risks observed for douching. This suggests that early adulthood may be a particularly important period to consider for the risks associated with these intimate care product exposures. Indeed, many established risk (or preventive) factors of ovarian cancer occur during early adulthood, including contraception, parity, and breastfeeding.<sup>19-22</sup> In addition to highlighting this critical window of risk, O'Brien et al<sup>18</sup> have illustrated a method for addressing the potential role of exposure misclassification when reporting results in epidemiologic studies. While the degree of bias is unknown, the reader can make their own assessment about the reasonable range of realistic risks based on the misclassification scenarios provided. In this paper, even with misreporting of the exposure (ie, genital powder use) in half the cases, a significant increase in ovarian cancer risk is still observed, adding support to the plausibility of a true association between genital powder use and ovarian cancer risk.

## ACCOMPANYING CONTENT

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## THE TAKEAWAY

In the article that accompanies this editorial, O'Brien et al<sup>18</sup> use a variety of methods to address the impact of bias on the association between intimate care products and hormone-related cancers (ovarian, uterine, and breast)—observing that genital powder use and douching were each associated with ovarian cancer risk even after accounting for multiple bias scenarios. Given that genital powder use and douching are modifiable exposures potentially associated with a highly fatal disease, these data suggest that people at risk for ovarian cancer, particularly those in their 20s and 30s, should be made aware of the potential risks.

There remain challenges in studying intimate product use, particularly genital powder, and ovarian cancer risk. Since 2014, multiple lawsuits have been filed against companies that sold talcum powder products alleging that ingredients or contaminants of these products played a role in causing ovarian cancer. In light of media attention related to these lawsuits, awareness of potential harm due to genital powder use is much more common and limits the ability for unbiased exposure reporting from those with and without disease. This has made the issue of recall bias particularly important for contemporary case-control studies<sup>23</sup> and prospective cohorts<sup>18</sup> that have collected data on genital powder use after media coverage of the lawsuits. People with ovarian cancer may be more likely to report any genital powder use as they are aware it could have contributed to their disease while those without ovarian cancer may not report genital powder use as thoroughly or at all, leading to an overestimate of the association. To address this issue, O'Brien et al<sup>18</sup> considered a range of possible exposure misclassifications by both the cases and the controls and recalculated the results to show that even with a fairly large degree of exposure misclassification the association persists (though attenuated), suggesting that this type of bias cannot fully explain the results.

This study also adds to the sparse literature on intimate care product use and uterine and breast cancer risks,<sup>24–26</sup> with no association observed between genital powder or douching and uterine or breast cancer. Given that ovarian and uterine cancers are both gynecologic cancers and the reported association with one but not the other may not be appreciated by the general population, one could expect them to be similarly affected by recall bias. Thus, the lack of an association between genital powder use and uterine cancer

provides additional support that recall bias does not fully explain the genital powder and ovarian cancer association.

One limitation of this study, as is the case for most prospective cohorts, is that due to the rarity of ovarian cancer, power is limited to examine associations by ovarian cancer histotype. The authors stratified by serous versus nonserous, reporting stronger associations for the serous histotype in analyses with and without recall bias correction, although the confidence intervals did overlap between the two histotype groups. These results are consistent with previous studies which show relatively consistent results for serous ovarian cancers and less consistency across other histotypes, likely due to smaller case numbers in these subgroups.<sup>16</sup> Given that high-grade serous is the most common and one of the most fatal of the ovarian cancer histotypes and has had fewer identified risk factors than other histotypes (eg, endometrioid),<sup>27</sup> these results suggest that genital powder use and douching may be modifiable risk factors and provide some insight into the underlying etiology for this histotype.

Looking forward, given that genital powder use and douching are modifiable exposures likely associated with a highly fatal disease, these data suggest that people at risk of ovarian cancer, particularly those in their 20s and 30s, should be made aware of the potential risks while also recognizing that the absolute risk of ovarian cancer remains low.<sup>16</sup> Primary care providers and gynecologists should consider addressing routine genital powder use and douching with their patients in a manner that addresses potential risks but also acknowledges the motivations behind intimate product use<sup>4,9,10</sup> to more effectively influence behavior change.

## AFFILIATIONS

<sup>1</sup>Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA

<sup>2</sup>Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA

<sup>3</sup>Department of Public Health, University of West Florida, Pensacola, FL

<sup>4</sup>Department of Obstetrics and Gynecology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

<sup>5</sup>Boston Center for Endometriosis, Boston Children's Hospital and Brigham and Women's Hospital, Boston, MA

<sup>6</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

## CORRESPONDING AUTHOR

Holly R. Harris, ScD, MPH; e-mail: hharris@fredhutch.org.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHOR CONTRIBUTIONS

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Epidemiologic Methods to Advance Our Understanding of Ovarian Cancer Risk**

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**Kathryn L. Terry**

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